76. *The Oxidation of* cyclo*Hexanone and Suberone by Means of Caro's Acid.*

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THE convenient preparation of 6-hydroxyhexoic and 7-hydroxyheptoic acids or their simple derivatives has become an object of investigation in connection with two different synthetical investigations in this laboratory. Many-stage syntheses have been proposed, and even recently used, in the case of 6-hydroxyhexoic acid, but these are obviously unsatisfactory in connection with such a simple substance. The most promising line of attack is the development of the method of Baeyer and Villiger (*Ber.*, 1899, **32**, 3625; 1900, **33**, 858) whereby ketopolymethylenes are oxidised by Caro's acid or an equivalent reagent. From suberone, for example, Baeyer and Villiger obtained, in the presence of alcohol, ethyl 7-hydroxyheptoate in a yield of 40%. Careful repetition of this work has made it clear that the reaction is more complex than would appear from the description. Under the specified conditions, carefully observed, the product was a mobile oil having an agreeable odour of pineapples, but this could not be distilled even in a high vacuum. The resulting very viscous material, after hydrolysis with alkali and treatment with hydriodic acid, afforded 7-iodoheptoic acid (the position of the iodine should perhaps be regarded as uncertain). Hence it seemed that the complex substances obtained on attempted distillation of the primary product were poly-esters. Accordingly, we modified the process as described by Baeyer and Villiger by adding a stage of re-esterification of the crude product by means of boiling alcoholic sulphuric acid. Ethyl 7-hydroxyheptoate could then be isolated, but even so the yield was sensitive to the conditions of the oxidation and especially to the temperature. At 0° some suberone peroxide was formed and some unchanged ketone was recovered; the best temperature was near 15°. It is not improbable that some manipulation equivalent to our re-esterification was actually employed by Baeyer and Villiger and thought to have little significance.

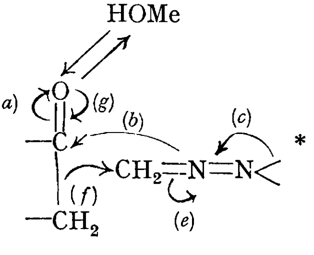
The oxidation of *cyclo*hexanone by the Baeyer–Villiger general method was first examined by Linstead and Rydon (J., 1934, 1999), who stated that the product was a high-boiling oil which could not be distilled without decomposition. This observation has been confirmed, but treatment of the crude product with boiling alcoholic sulphuric acid affords ethyl 6-hydroxyhexoate in useful yield, and for the first time the ω-substituted hexoic acids become readily accessible substances. Similarly, hexamethylene glycol becomes more available by applying the Bouveault–Blanc reduction method to the hydroxy-ester. We were unable to discover a satisfactory method for the oxidation of 4-methyl*cyclo*hexanone by Caro's acid.

The oxidation of *cyclo*pentanone proceeds with eventual formation of *ethyl* 5-*hydroxyvalerate* in only moderate yield. The ester is mixed with an unsaturated by-product; there is a little of such a substance in the ethyl 6-hydroxyhexoate obtained as here described, but the specimen of ethyl 7-hydroxyheptoate was saturated.

The elegant method of Mosettig and Burger (*J. Amer. Chem. Soc.*, 1930, **52**, 3456) superseded all earlier processes for the preparation of suberone. We have found it convenient to adopt a few modifications in detail, and have isolated 1-hydroxymethyl*cyclo*hexan-1-ol as a by-product of the action of diazomethane on *cyclo*hexanone in the presence of methyl alcohol and subsequent to the treatment of the products with aqueous sodium bisulphite. It seems probable that this glycol arises from the hydration of the corresponding ethylene oxide derivative obtained by Mosettig and Burger as a by-product (*loc. cit.*).

For the mechanism of this and similar ring enlargements, Mosettig and Burger approve the hypothesis of Meerwein and of Arndt involving the migration of radicals or their equivalent in the form of full free valencies. It seems, however, that the course of the process can be illustrated without making such an assumption if we combine the suggestions of Bradley and Robinson (J., 1928, **1312**) with the idea of electromeric vibrations of small, possibly very small, amplitude (Robinson, *Chem. News*, 1926, **133**, 7). The reaction occurs only in the presence of methyl alcohol, here regarded simply as a source of active proton, free or combined, which by reversible co-ordination with the oxygen of the carbonyl group through the unshared electrons of the oxygen atom initiates the process by inducing the electromeric change (*a*). This excitation of the carbonyl group by the catalyst results in an electron defect on the carbon atom, which is remedied by the attack of unshared electrons of the diazomethane (*b*).

The displacement (*b*) and its corollary (*c*) doubtless occur to some extent in the normal molecules, but go further when the strain on the carbon atom of the diazomethane is relieved in the course of reaction. Both are steps in the formation of the nitrogen molecule, which now asserts its autonomous character by taking charge of the electrons necessary for its independent existence (*e*). This produces, however, a defect of electrons on the diazomethane carbon, which must in consequence acquire other electrons from the oxygen atom (ethylene oxide formation, not represented) or from the nearest bond in the *cyclo*hexane ring (*f*). The latter change is synchronous with, or closely followed by, the reversal of (*a*), namely, (*g*). Alternations of (*a*) and (*g*) together with the unidirectional displacements (*b*)—(*f*) bring about the completion of the reaction in a continuous manner.



EXPERIMENTAL.

Suberone.—The method was essentially that of Mosettig and Burger (*loc. cit.*) with some improvements in the manipulation such as the use of more efficient fractionating columns and slight variations in the method of working up the product. *cyclo*Hexanone (73·2 g.) gave suberone (46·0 g., b. p. 67—68°/12 mm.), and the material that did not react with sodium bisulphite was fractionated as follows at 13—14 mm.: (1) 1·3 g., b. p. 40—74°; (2) 1·0 g., b. p. to 93°; (3) 0·8 g., b. p. to 100°; (4) 4·0 g., b. p. to 115°; (5) 1·8 g., b. p. 118—123°; (6) 6·0 g., b. p. to 132°; (7) 2·5 g., b. p. to 140°; (8) 2·8 g., b. p. 150—155°.

All fractions except (5) and (6) were liquid, and (1), (2), and (3) were ketonic (ready formation of dinitrophenylhydrazones); (2) was largely *cyclo*octanone, identified by the preparation of the semicarbazone and 2 : 4-dinitrophenylhydrazone (compare Mosettig and Burger). Fractions (5) and (6) solidified, and (6) was crystallised from benzene–light petroleum, forming colourless needles, m. p. 73·5—74° (Found: C, 64·8; H, 10·8. Calc. for $C_7H_{14}O_2$: C, 64·6; H, 10·7%). The substance is readily soluble in water, and in organic solvents with the exception of light petroleum. When heated in dilute sulphuric acid solution with potassium permanganate, *cyclo*hexanone was formed, and identified by analysis and by the preparation of the semicarbazone, m. p. 161—162° and m. p. 162—163° when mixed with an authentic specimen, m. p. 164—164·5°. The semicarbazone of suberone has m. p. 163—164°, but a mixture with *cyclo*hexanone semicarbazone shows a depression of 20°. This by-product is evidently 1-hydroxymethyl*cyclo*hexan-1-ol, which has m. p. 76—77° (Wallach and Isaac, *Annalen*, 1906, **347**, 331).

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[*] This symbol was employed in 1928 in order to formulate the reactions of diazomethane on an electronic basis. It implies precisely the same view of the actual constitution of the substance as that based on the hypothesis of resonance, although it is certainly true that the latter theory suggests new ways of testing the validity of this and similar structures. The basic structural conceptions of the resonance theory in organic chemistry are not novel; what is new is the possibility of more searching analysis and the theoretical derivation and justification of the existing hypothesis of intermediate valency states.—R. R.

Ethyl 7-*Hydroxyheptoate.*—Potassium persulphate (50 g.) was gradually added to a well-stirred mixture of sulphuric acid (71 c.c., *d* 1·84) and water (24 c.c.) maintained below 15°; alcohol (100 c.c.) was then introduced, also below 15°. The temperature being kept *at* 15°, a mixture of suberone (10 g.) and alcohol (30 c.c.) was added during 1 hour, and stirring was continued for a further 1½ hours. The mixture was diluted to 1 litre, filtered, saturated with ammonium sulphate, and thoroughly extracted with ether. After removal of the solvent from the dried extract, the residue was mixed with alcohol (15 c.c.) and sulphuric acid (1 c.c.) and heated (bath at 110°) for 6 hours. The product was isolated by means of ether and distilled, b. p. 140—146°/12 mm. (nearly all at 142°) (7·5 g.), with a clear brown oily residue, b. p. 193°/0·5 mm. (Found : C, 64·3; H, 10·4. $C_{16}H_{30}O_5$ requires C, 63·6; H, 9·9%). This *substance* appears to be a di-ester of the formula $OH\cdot[CH_2]_6\cdot CO\cdot O\cdot[CH_2]_6\cdot CO_2Et$, since it furnished the hydrazide described below.

The main fraction, ethyl 7-hydroxyheptoate, afforded a *phenylurethane*, glistening white plates from light petroleum, m. p. 64—65° (Found : N, 4·9. $C_{16}H_{23}O_4N$ requires N, 4·8%), and a *hydrazide*, which crystallised from ethyl acetate as silky white needles, m. p. 121—123° (Found : N, 17·6. $C_7H_{16}O_2N_2$ requires N, 17·5%). In some experiments, under other conditions, the odour of pineapples was very pronounced, and in such cases the yield was diminished. The substance responsible for the odour is a volatile solid which we have not examined because our object was to avoid its formation. Taking into consideration the work of Natta, Hill, and Carothers (*J. Amer. Chem. Soc.*, 1934, **56**, 455) on the 14-membered ring dilactone related to 6-hydroxyhexoic acid, and of Ruzicka and Stoll (*Helv. Chim. Acta*, 1928, **11**, 1159) on the relation between odour and number of ring-members in large-ring lactones, it seems certain that this volatile odoriferous solid is the 16-membered ring dilactone related to 7-hydroxyheptoic acid.

Ethyl 6-*Hydroxyhexoate.*—The oxidising mixture was prepared as described above but with double quantities, and it was adjusted to 10°. *cyclo*Hexanone (19 g.) in alcohol (30 c.c.) was then added during 1 hour, and after a further 15 minutes the cooling bath was removed and stirring continued for 1 hour; the temperature finally reached was 15°. The product was isolated as in the previous case, then mixed with alcohol (50 c.c.) and sulphuric acid (4 c.c.) and refluxed for 6 hours. The esters were isolated as before, and on distillation, ethyl 6-hydroxyhexoate (14·7 g.), b. p. 134°/15 mm. (Found: C, 60·2; H, 9·9. Calc. for $C_8H_{16}O_3$: C, 60·0; H, 10·0%), was obtained; the residue was a pale yellow oil (3 g.), b. p. 158—160°/0·05 mm. or 191°/1·5 mm. (Found: C, 61·3; H, 9·4. $C_{14}H_{26}O_5$ requires C, 61·3; H, 9·5%), evidently consisting of 5-*carbethoxyamyl* 6-*hydroxyhexoate*, $OH\cdot[CH_2]_5\cdot CO\cdot O\cdot[CH_2]_5\cdot CO_2Et$.

Ethyl 6-hydroxyhexoate forms a *phenylurethane*, white plates, m. p. 50—51° (Found : N, 5·1. $C_{15}H_{21}O_4N$ requires N, 5·0%), from light petroleum. In agreement with Natta, Hill, and Carothers (*loc. cit.*), the hydrazide had m. p. 115° and was also obtained from the above di-ester.

The method works well on a large scale; *cyclo*hexanone (95 g.) oxidised at 10° gave ethyl hydroxyhexoate (60 g.).

Small quantities of cyclo*hexanone peroxide* were formed in some of our experiments and constituted the solid precipitated when the oxidation mixture was diluted; the specimens, combined and crystallised from benzene, gave prisms, m. p. 128° (Found: C, 63·4; H, 8·8. $C_6H_{10}O_2$ requires C, 63·2; H, 8·8%). The substance had the usual character of ketone-peroxides; it was stable towards acid solutions of potassium iodide, but a red coloration gradually appeared when a solution in light petroleum was shaken with aqueous ferrous sulphate and ammonium thiocyanate.

Hexamethylene Glycol.—A mixture of ethyl hydroxyhexoate (12·5 g.) and anhydrous alcohol (50 c.c.) was rapidly added to sodium (10·8 g.) (bath at 140°) with the usual arrangements. After the initial reaction, more alcohol and then water were introduced, and the mixture was eventually acidified with hydrochloric acid, saturated with ammonium sulphate, and extracted with ethyl acetate. The product (6·0 g.) had b. p. 145—146°/16 mm., and solidified at once on cooling (cf. Bouveault and Blanc, *Bull. Soc. chim.*, 1904, **31**, 1204). A procedure analogous to that recommended in " Organic Syntheses " (**1**, 8) for the preparation of trimethylene bromide being adopted, the glycol (5·8 g.) gave hexamethylene dibromide (8·7 g., b. p. 110°/12 mm.) (steam-distillation of the dibromide would probably be an improvement).

Ethyl 5-*Hydroxyvalerate.*—The oxidation of *cyclo*pentanone (10 c.c.) was effected as described above but at —5° to 2°. After all the stages detailed above had been followed, *ethyl* 5-*hydroxyvalerate* (4·5 g.), b. p. 114°/14 mm., was isolated (Found: C, 58·5; H, 9·3. $C_7H_{14}O_3$ requires C, 57·5; H, 9·6%). The *hydrazide*, crystallised from ethyl acetate, had m. p. 105—106° (Found :

N, 20·9. $C_5H_{12}O_2N_2$ requires N, 21·2%). The high value for carbon in the case of the ester was found to be due to the presence of an unsaturated impurity.

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